REMARKS

Formal Matters

Claims 5-10, 14, 15, 18 and 19 were examined and stand rejected. Claims 5-7, 14-15 and 18-19 have been canceled.

Claims 8-10 and 27-28 are pending after entry of the amendments set forth herein.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Support for the amendments to claims can be found throughout the specification and in particular, at page 10, lines 26-31 through page 11, lines 1-2; page 48, lines 1-26. As such, no new matter has been added.

Specification

The specification was objected to because the Office Action asserted the following informalities: "in the Brief Description of the Drawings, page 8, line 4 should begin with '3B' not '2B' [and] page 47, line 10 refers to Figure 2. The targeting construct is depicted in Figure 3, not Figure 2." The Applicants have corrected page 8, line 4 and page 47, line 10 by providing replacement paragraphs. Applicants submit that no new matter has been introduced into the application and that the informalities are overcome in view of this amendment.

Rejection under 35 U.S.C. § 112, 1st paragraph.

Claims 5-9, 14, 15, 18-19 stand rejected under 35 U.S.C. § 112, 1st paragraph. Claims 5-7, 14-15 and 18-19 have been canceled. As such, the rejection with respect to these now-canceled claims is moot.

With respect to pending claims 8-10, it is asserted in the Office Action that the specification does not provide an adequate written description for or enable the claimed invention for any and all NOR1 genes other than NOR1 gene encompassed by SEQ ID

NO: 1. (Office Action, page 9) Specifically, the Office Action asserts that the specification, while being enabling for a knockout mouse with a homozygous disruption in a NOR1 gene identified as SEQ ID NO: 1 wherein said mouse exhibits increased or enhanced pain threshold or impaired balance and impaired motor coordination, a method of making said mouse by introducing a knockout construct into an embryonic stem cell, does not reasonably provide enablement or adequate written support for a transgenic mouse comprising **any type** of disrupted NOR1 gene having **any phenotype** other than increased or enhanced pain threshold or impaired balance and impaired motor coordination and a method of making the knockout mouse by introducing a knockout construct into **any type** of cell.

In connection with this rejection, the Examiner states that "limiting claims 5-9, 14 and 15 to a transgenic mouse or mouse cell and deleting 'a' preceding 'NOR1' in claims 5, 8, 18-19 would overcome this rejection." Further, the Examiner states "the claims should be limited to a homozygous disruption of the NOR1 gene." Applicants have adopted Examiner's suggested modifications, or addressed Examiner's rejection, by: (1) limiting the above-mentioned claims to a transgenic mouse or mouse cell and deleting 'a' preceding NOR1; (2) inserting homozygous to describe the type of disruption in the NOR1 gene; (3) reciting the specific type of cell (i.e., mouse ES cell) into which the knockout targeting construct is introduced; and (4) inserting phenotypic language into the pending amended claims such that the transgenic mouse having a homozygous disruption in NOR1 exhibits increased or enhanced pain threshold or impaired balance and impaired motor coordination.

In light of the foregoing, Applicants submit that the rejections of the above-cited claims under 35 U.S.C. § 112, first paragraph, both as to enablement and written description, are overcome in view of the amendments, claim cancellations, and remarks set forth herein. The Examiner is thus respectfully requested to withdraw these rejections.

Rejection under 35 U.S.C. § 103(a).

Claims 5-8 and 10 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Capecchi (Scientific American, 1994, vol. 270, pp 34-41) in view of Maltais (February 2000, DNA and Cell Biology, Vol. 10, pages 121-130). Applicants respectfully traverse this rejection. However, in view of the cancellation of claims 5-7 and in view of the amendments to the pending claims, Applicants submit that the rejection under 35 U.S.C. § 103 is no longer relevant.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) **must teach or suggest all the claim limitations**. See MPEP §2143.

According to the Examiner, Capecchi discloses transforming a cell with a nucleic acid construct comprising a disruption in the *Hox*A-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous *Hox*A-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the *Hox*A-3 gene. Capecchi very generally discusses the method of targeted gene replacement, specifically as it relates to disrupting the *Hox*A-3 gene. Capecchi then further specifically discusses the effect or phenotype of a knockout of the *Hox*A-3 gene in mice observed in his laboratory, which revealed a role for *Hox*A-3 in development of the mouse embryo.

Maltais, as characterized by the Examiner, teaches the cloning and characterization of the mouse TEC (NOR1) gene. The Examiner relies on the teachings of Maltais to provide motivation to disrupt the NOR1 gene.

However, neither Capecchi nor Maltais, alone or in combination, teaches all of the limitations as presently claimed. As acknowledged by the Examiner, Capecchi provides no disclosure or teaching of how to make a NOR1gene knockout mouse. More particularly, Capecchi does not disclose a transgenic mouse comprising a disruption in a NOR1gene, wherein the transgenic mouse exhibits a specific phenotype, particularly a phenotype of a increased or enhanced pain threshold or impaired balance and impaired motor coordination, as presently claimed. Likewise, Maltais does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in a NOR1

gene. More particularly, the disclosure of Maltais fails to provide any teaching or suggestion that relates to transgenic mice or cells, and in particular to those transgenic mice and cells as recited in the pending claims.

Taken together, the disclosures of Capecchi and Maltais are devoid of any teaching or suggestion of disrupting the NOR1 gene, and in particular, are deficient of any teachings or suggestions of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Capecchi and Maltais, alone or combined, do not teach or suggest in any way transgenic mice comprising disrupted NOR1 genes, wherein such transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of a increased or enhanced pain threshold or impaired balance and impaired motor coordination as claimed by the present invention.

The references, either alone or combined as suggested by the Examiner, fail to make obvious the claimed invention "absent any phenotypic requirements for the claimed transgenic mouse." As amended, the claims describe phenotypic abnormalities for the transgenic mice including increased or enhanced pain threshold or impaired balance and impaired motor coordination.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 5-7, and in view of the amendments to claims 8-10 and new claims 27-28, the currently pending claims are not obvious in view of the teachings of Capecchi and Maltais, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

Claims 5-10 and 14, 15, 18 and 19 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Beach (1999, USPN 5,919,997) in view of Maltais (February 2000, DNA and Cell Biology, Vol. 10, pages 121-130). Applicants respectfully traverse this rejection. However, in view of the cancellation of claims 5-7, and in view of the amendments to claims 8-10 and new claims 27-28, Applicants submit that the rejection under 35 U.S.C. § 103 is no longer relevant to the currently pending claims.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary

reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) **must teach or suggest all the claim limitations**. See MPEP §2143.

As amended, the claims describe phenotypic abnormalities for the transgenic mice including increased or enhanced pain threshold or impaired balance and impaired motor coordination.

According to the Examiner, Beach discloses transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous INK4 locus, and using said cell to generate a knockout mouse whose genome comprises a disruption in the INK4 gene. According to the Examiner, Beach discloses administering compounds to the transgenic knockout mice comprising a disruption in the INK4 gene to screen for agents that affect the INK4 mutant phenotype and modulate expression or function of INK4.

Maltais, as characterized by the Examiner, teaches the cloning and characterization of the mouse NOR1 gene. The Examiner relies on the teachings of Maltais to provide motivation to disrupt the NOR1 gene.

However, neither Beach nor Maltais , alone or in combination, teaches all of the limitations as presently claimed. In particular, Beach does not disclose a transgenic mouse comprising a disruption in a NOR1 gene, wherein the transgenic mouse exhibits a specific phenotype, particularly a phenotype of a increased or enhanced pain threshold or impaired balance and impaired motor coordination, as presently claimed. Likewise, Maltais does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in a NOR1 gene. More particularly, the disclosure of Maltais fails to provide any teaching or suggestion that relates to transgenic mice or cells, and in particular to those transgenic mice and cells as recited in the pending claims.

Taken together, the disclosures of Beach and Maltais are devoid of any teaching or suggestion of disrupting the NOR1 gene, and in particular, are deficient of any teachings or suggestions of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Beach and Maltais , alone or combined, do not teach or suggest in any way transgenic mice comprising disrupted NOR1 genes, wherein such

transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of a increased or enhanced pain threshold or impaired balance and impaired motor coordination as claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 5-7, and in view of the amendments to claims 8-10 and new claims 27-28, Applicants submit that the currently pending claims of the present application are not obvious in view of the teachings of Beach and Maltais, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

Conclusion.

Applicants submit that all of the pending claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1271.

Respectfully submitted,
DELTAGEN, INC.

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